UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/842,369	04/26/2001	Leonard Buckbinder	PC10758	7986

7590 02/14/2003

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EXAMINER
MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
1652	10

DATE MAILED: 02/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/842,469	BUCKBINDER ET AL.
Examiner	**Art Unit**
William W. Moore	1652

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-4,7-13 and 15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
4) ☐ Interview Summary (PTO-413) Paper No(s).
5) ☐ Notice of Informal Patent Application (PTO-152)

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse in Paper No. 9 filed November 18, 2002, of the Invention of Group 6, comprising claims 5 and 6 and, in part, claim 14, to the extent that these claims describe a human ADAMTS-E polypeptide having the amino acid sequence set forth in SEQ ID NO:2, its four component domains, and to a method of use thereof in identifying compounds which inhibit the activity of a human ADAMTS-E polypeptide, is acknowledged.

Claim Rejections - 35 USC § 101

35 U.S.C. §101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 5, 6 and 14 are rejected under 35 U.S.C. §101 because the claimed invention of claims 5 and 6 is directed to non-statutory subject matter and also because the claimed invention of claims 5, 6 and 14 lacks patentable utility.

Claims 5 and 6 describe a product of Nature, in Nature, hence cannot describe a product made by a person as required by 35 U.S.C. §101. Where claim 5 describes "[a] polypeptide encoded by the isolated polynucleotide molecule of claim 1", it fails to distinguish a claimed product from a native ADAMTS-E occurring naturally in human cells and claim 6 does not improve the description of claim 5. Should the specification provide support for description of "an isolated", or of "a purified", polypeptide, amending claim 5 with either term to describe a polypeptide removed from Nature will overcome this aspect of the rejection.

A claimed invention must posses a specific, substantial and credible *in vitro* or *in vivo* utility. It is agreed that the amino acid sequence of the human ADAMTS-E, SEQ ID

to have been identified as an aggrecanase. It is also agreed that Example 2 at pages 25

and 26 of the specification discloses that mRNA transcripts specifying the ADAMTS-E polypeptide are expressed in several human tissues, e.g., heart, spleen, kidney, liver, brain, and lung, as well as in chondrocytes of osteoarthritic human cartilage. The specification fails to demonstrate, however, that the ADAMTS-E polypeptide can recognize and act on any specific substrate, not even aggrecan. Because there is no indication that the level of expression of the ADAMTS-E transcript differs from chondrocytes present in normal joint cartilage and those present in osteoarthritic cartilage, there is no indication that ADAMTS-E polypeptides have any specific physiological role in health or in disease, neither is there any indication of any specific cellular or extracellular role that the ADAMTS-E polypeptide might play, whether in cardiomyocytes or chondrocytes. While the specification proposes potential diagnostic, prognostic, treatment, and screening uses, both *in vitro* and *in vivo*, for a native ADAMTS-E – which uses may be substantial if they were they specific and demonstrated – the specification fails to identify a **specific** and substantial utility for the elected subject matter of claims 5, 6 and 14 at the time the application was filed.

A method of use of a material for further research to determine, e.g., its specific biological role, thus identifying or confirming a "real world" context for its use, cannot be considered to be a "substantial utility". *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). Mere allegations of a prospective, potential, utility cannot rise to the level of a credible assertion of a **specific** *in vivo* utility that is substantial and mere sequence similarity cannot support a **specific** *in vitro* utility that is substantial. Indeed, the specification's diffuse assertions indicate the contrary: that Applicant knew no specific utility for a native human ADAMTS-E polypeptide at the time the application was filed that would permit its immediate use by the public. In order to overcome this aspect of the

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 6 and 14 are also rejected under 35 U.S.C. §112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 5, 6 and 14 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe the preparation of the subject matters of divergent ADAMTS-E polypeptides of claims 5 and 6 and a method of use of claim 14. This is because generic proteins of claims 5 and 6, and a method of use of such a generic protein of claim 14, are based on a very broad genus of polynucleotides that differ from a nucleic acid sequence encoding SEQ ID NO:2 herein at as much as 20% of the nucleotide sequence positions. Where the variations occur at initial codon positions in the nucleotide sequence, this permits a divergence in coding capacity at as many as 60% of the codons that specify the amino acid sequence of SEQ ID NO:2. Thus members of the genus of polypeptides may differ at as many as 60% of the amino acid positions from the amino acid sequence of SEQ ID NO:2, and claim 6 does no more than shift the locations for the regions of variation from one domain to another of the ADAMTS-E polypeptide of SEQ ID NO:2. Yet neither the specification nor the claims describe where any difference in the amino acid sequence of SEQ ID NO:2 might occur, or what the difference might be. The

[illegible] proteins that meet the [illegible]

out one's invention before filing a patent application, one does need to be able to describe

that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification furnishes no relevant identifying characteristics of such polypeptides diverging at as many as 662 amino acid positions from the 1104-amino acid sequence of SEQ ID NO:2, nor does it provide any characteristic permitting a correlation between undisclosed structures of the myriad species of generic proteins of claims 5 and 6 and the disclosed amino acid sequences of SEQ ID NO:2.

The Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Indeed, like the claims invalidated by the appellate panel in *University of California v. Eli Lilly*, the claims rejected herein were designed to embrace other, as yet unknown, human and mammalian polypeptides. Nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of any of these undisclosed generic proteins to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The specification's treatment of the claimed subject matter is considered to be entirely prospective where skilled artisans in the relevant field of molecular biology could not predict the structure, or other properties, of the claimed generic polypeptides.

Claims 5, 6 and 14 are rejected under 35 U.S.C. §112, first paragraph, because the specification is not enabling for any embodiment of human protease having an amino acid sequence that differs from the amino acid sequence of SEQ ID NO:2 by [illegible] person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

This rejection is separate from the rejection stated above stated under the first paragraph of the statute for lack of enablement as to use of even a disclosed ADAM-TS polypeptide having the 1104-amino acid sequence of SEQ ID NO:2. Claims 5 and 6 contemplate arbitrary assignments of any or all of amino acid substitutions, additions or deletions in a galaxy of generic polypeptides bounded by an upper limit of 662 amino acid variations from the ADAMTS-E primary structure set forth in the 1104-amino acid sequence of SEQ ID NO:2. The specification cannot support introduction of even a few amino acid insertions, deletions, or substitutions in the amino acid sequence of SEQ ID NO:2, where these alterations may occur anywhere, in any combination or any pattern, in the amino acid sequence set forth in SEQ ID NO:2. Indeed, neither the prior art made of record herewith nor in Applicant's Information Disclosure of Paper No. 6 can identify, taken together with the specification, a few amino acids in the primary sequences of members of the family of human ADAMTS metalloproteases that might be altered, nor teach the nature of an alteration that may be made, which permits a resulting polypeptide to support its native function. Mere sequence perturbation cannot enable the design and preparation of nucleotide sequences encoding a myriad of divergent protease enzymes and provide the public with a nucleotide sequence encoding an enzyme that retains its native function. This is well demonstrated by the publication of Seffernick et al., 2001, Journal of Biochemistry, Vol. 183, pages 2405-2410, made of record herewith, who teach that the alteration of 9 amino acids in a sequence of 475 amino acids, a scant 2% of the native amino acid positions, in a deaminase will suffice to alter its substrate specificity and require it to catalyze different reactions even though, p. 2409, these alterations do not at all alter its tertiary structure and are spread throughout its primary structure.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be

Without undue experimentation and that unpredictability in an attempt to practice a

claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide hormone); see also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure only of a single B-cell growth factor allele). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997).

The Federal Circuit has also considered whether definitional statements might enable a claim scope argued to extend beyond a disclosed gene product having its native amino acid sequence to embrace a specific variant gene product encoded by a specifically-altered DNA sequence. *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994). The court held that only a narrow structural and functional definition was enabling precisely because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech*, 29 F.3d 15 at 1564-65, 31 USPQ2d at 1168. Applying the "*Forman*" factors discussed in *Wands*, *supra*, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate specific guidance for altering the amino acid

the extent recited in the claims,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no members of the class of human ADAMTS metalloproteases represented by the amino acid sequence of SEQ ID NO:2, have had even a few amino acids specifically identified for concurrent modification to maintain their native function.

Thus the scope of subject matters embraced by claims 5, 6 and 14 is unsupported by the present specification even if taken in combination with teachings available in the prior art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 5, 6 and 14 are rejected under 35 U.S.C. §102(e) as being anticipated by Apte et al., U.S. Patent No. 6,391,610, made of record herewith.

Apte et al.('610) is the counterpart of WO 01/11074, made of record with Applicant's Information Disclosure Statement and discloses amino acid sequences of several human zinc metalloproteases related to the ADAMTS family including SEQ ID NO:17, the amino acid sequence of the ADAMTS-10 metalloprotease, which shares 88% identity with the amino acid sequence of the human ADAMTS-E polypeptide depicted in SEQ ID NO:2 herein and encoded by a nucleic acid sequence set forth in SEQ ID NO:16 of the '610 patent which is 93% identical to SEQ ID NO:1 herein and 97% identical thereto

amino acid sequences of the disintegrin domain and the first thrombospondin (TSP) motif

of the ADAMTS-10 of the '610 patent are identical to the amino acid sequences of the disintegrin domain and the first thrombospondin (TSP) motif of SEQ ID NO:2 herein, meeting limitations of claim 6 herein. Apte et al. further disclose, col. 6 at lines 20-42, use of the ADAMTS polypeptides in assays to identify compounds capable of inhibiting ADAMTS polypeptide activity in which at least a purified composition of a candidate ADAMTS polypeptide is contacted with a candidate inhibitory compound and the extent of inhibition determined, meeting limitations of claim 14 herein.

Claims 5, 6 and 14 are rejected under 35 U.S.C. §102(e) as being anticipated by Heller et al., published U.S. patent Application No. 2002/0107361, made of record herewith.

Based on disclosures of their February 18, 2000-filed U.S. Provisional application, Heller et al. disclose the amino acid sequences of several human zinc metalloproteases related to the ADAMTS family including SEQ ID NO:3, the amino acid sequence of their MPTS-10 metalloprotease which shares 72.3% identity with the amino acid sequence of the human ADAMTS-E polypeptide depicted in SEQ ID NO:2 herein and encoded by a nucleic acid sequence set forth in SEQ ID NO:4 of the '361 publication which is 88.8% identical to SEQ ID NO:1 herein and 97% identical thereto between positions 138 and 1,596, inclusive, as well as between positions 1,810 and 2,569, inclusive, meeting limitations of claim 5 herein. The amino acid sequences of the signal peptide, prodomain, and protease domain MPTS-10 of the '361 patent publication are identical to the amino acid sequences of the signal peptide, prodomain, and protease domain of SEQ ID NO:2 herein, meeting limitations of claim 6 herein. Heller et al. also meet limitations of claim 14 herein in disclosing, see paragraphs 0080 through 0087 at page 9 of the publication, use of MPTS polypeptides in assays to identify compounds capable of inhibiting MPTS polypeptide activity in which a purified composition of a candidate MPTS polypeptide is

Allowable Subject Matter

While both of the published U.S. patent applications of Kappeller-Libermann et al., US 2002/0072490 and US 2002/0076778, and the published International Applications of Plowman et al., WO 01/93782, and of Racie et al., WO 02/34895, disclose human zinc metalloproteases having amino acid sequences which meet limitations of claims 5 and 6 herein where they are encoded by polynucleotides exceeding 80% identity with nucleic acid sequence disclosed to encode SEQ ID NO:2 herein – indeed SEQ ID NO:9 of Kappeller-Libermann et al., '490 differs at but one amino acid position, 134, within the first 1,044 amino acids of SEQ ID NO:2 herein – all were based on U.S. Provisional applications filed after Applicant's April 26, 2000, filing date for the provisional application to which priority is claimed herein. Thus, demonstrating that a specific activity is disclosed for the subject matter elected herein and amending claim 5 to describe the native ADAMTS-E having the amino acid sequence of SEQ ID NO:2, and amending claim 6 to describe a polypeptide **consisting of** at least that series of domains within SEQ ID NO:2 for which both a specific utility is demonstrable and an integral amino acid sequence of SEQ ID NO:2 exceeds the identical disclosures of domains of related, prior art, ADAMTS polypeptides may permit allowance of claims to such discrete subject matters.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM-5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. The examiner's direct FAX telephone number is 703.746.3169. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
February 7, 2003